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10/691,653	10/24/2003	Jean-Louis Escary	60711.000024	7953
21967 7590 05/15/2007 HUNTON & WILLIAMS LLP INTELLECTUAL PROPERTY DEPARTMENT 1900 K STREET, N.W. SUITE 1200 WASHINGTON, DC 20006-1109			EXAMINER SEHARASEYON, JEGATHEESAN	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/20/2007 has been entered. An action on the RCE follows.

2. Claims 37 and 40 are amended. Claims 26, 29-36, 38, 39, 40, 43-46, 49 and 50 are canceled. Claims 51-65 are newly added. Claim 40 remains withdrawn. Therefore, claims 27, 28, 37, 42, 47, 48 and 51-65 are examined.

3. Any objection or rejection of record, which is not expressly repeated in this action, has been overcome by Applicant's response and withdrawn.

4. Allowability of claims 27, 28, 42, 47 and 48 are withdrawn.

Specification

5a. The specification is objected to because of the recitation of tables without table numbers or titles (see pages 43-49).

5b. The use of the trademarks FACScalibur and CellQuest have been noted in this application (p. 45, paragraph 402). Trademarks should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent application, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Claim Objections

6. Claims 27, 28, 37, 42, 47, 48 and 51-65 objected to because as written, it is not clear if amino acid position 45 is relative to the start of the full-length SEQ ID NO: 2, or relative to the start of the polypeptide starting at amino acid 24 of SEQ ID NO: 2 (i.e. 45 amino acids from position 24 of SEQ ID NO: 2).

7. Applicant is advised that should claim 27 be found allowable, claims 51 and 57 will be objected to under 37 CFR 1.75 as being substantial duplicates thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, the claims are drawn to identical subject matter except for recited functional limitations of antiviral activity (claims 51 and 57). If found allowable, the polypeptide of claim 27 would also be expected to inherently possess anti viral, immunomodulatory and /or anti-proliferative activities.

8. Applicant is advised that should claim 28 be found allowable, claims 56 and 58 will be objected to under 37 CFR 1.75 as being substantial duplicates thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, the claims are drawn to identical subject matter except for recited functional limitations of antiviral activity (claims 56 and 58). If

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found allowable, the polypeptide of claim 28 would also be expected to inherently possess anti viral, immunomodulatory and /or anti-proliferative activities.

9. Applicant is advised that should claim 47 be found allowable, claims 59 will be objected to under 37 CFR 1.75 as being substantial duplicates thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, the claims are drawn to identical subject matter except for recited functional limitations of antiviral activity and anti-tumoral activity (claim 47). If found allowable, the polypeptide of claim 59 would be expected to inherently possess antiviral and anti-tumoral activities.

10. Applicant is advised that should claim 62 be found allowable, claims 63 will be objected to under 37 CFR 1.75 as being substantial duplicates thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, the claims are drawn to identical subject matter except for recited functional limitations of antiviral activity, anti-immunomodulatory activity and anti-proliferative activity (claim 63). If found allowable, the polypeptide of claim 62 would be expected to inherently possess all of these activities.

Claim Rejections - 35 USC § 112, first paragraph (new)

11a. Claims 27, 28, 42, 48, 51-58, 60, 61, 64 and 65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a written description rejection.*

The specification discloses isolated polypeptide G45R of SEQ ID NO: 2 or amino acids 24 thru 189 of SEQ ID NO: 2 or sequences that have 95-99% identity to SEQ ID NO: 2 or amino acids 24 thru 189 of SEQ ID NO: 2, with substitutions at wild-type positions generating SNPs wherein the resulting polypeptide exhibits antiviral activity against vesicular stomatitis virus (VSV) *in vitro* or antiviral activity against Encephalomyocarditis virus (EMCV) *in vivo* (mouse model) or cytokine release by CD4+ or CD8+ T-lymphocytes or cytokine release by monocytes or cellular antiproliferative activity on Daudi Burkitt's cell lines or cellular antiproliferative activity on TF-1 cell lines and any combination of the foregoing activities. This meets the written description of 35 USC 112, first paragraph. However, the specification does not disclose all possible polypeptides including portions or variants (resulting in amino acid residue changes generating 95% -99% homology) of SEQ ID NO: 2 or amino acids 24 through 189 of SEQ ID NO: 2 exhibiting all anti-viral or anti-tumoral or anti-proliferative or immunomodulatory activities. Applicants have claimed a genus of polypeptides that have no common function (polypeptide of SEQ ID NO: 2 that has anti-viral activity, anti-proliferative activity, immunomodulatory activity and anti-tumoral activity etc.). It is not

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clear what substitutions will retain common functions. Furthermore, the specification fails to disclose if a polypeptide with 95-99% homology containing SNPs G45R of SEQ ID NO: 2 or amino acids 24 through 189 of SEQ ID NO: 2 will be functionally similar to wild type containing the SNP of SEQ ID NO: 2 or amino acids 24 through 189 of SEQ ID NO: 2.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of SEQ ID number and the percent identity required and the broad recitation of function (e.g: anti-viral or anti-proliferative or anti-tumoral immunomodulatory). There is not even identification of any particular portion of the structure that must be conserved to retain the functions contemplated. Further, it is not clear if these functions are found together in variants or if these functional activities are found individually (see for example, claims 27 and 51). The claims as written, however, encompass SEQ ID NO: 2 variant sequences which were not originally contemplated and fail to meet the written description provision of 35 USC 112, first paragraph because the written description is not commensurate in scope with the recitation of claims 27, 28, 42, 48, 51-58, 60, 61, 64 and 65. Accordingly, in the absence of sufficient

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recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed” (See *Vas-Cath* at page 1116).

With the exception of isolated polypeptide G45R of SEQ ID NO: 2 or amino acids 24 thru 189 of SEQ ID NO: 2 or sequences that have 95-99% identity to SEQ ID NO: 2 or amino acids 24 thru 189 of SEQ ID NO: 2, with substitutions at wild-type positions generating SNPs wherein the resulting polypeptide exhibits antiviral activity against vesicular stomatitis virus (VSV) *in vitro* or antiviral activity against Encephalomyocarditis virus (EMCV) *in vivo* (mouse model) or dendritic cell maturation or cytokine release by CD4+ or CD8+ T-lymphocytes or cytokine release by monocytes or cellular antiproliferative activity on Daudi Burkitt's cell lines or cellular antiproliferative activity on TF-1 cell lines and any combination of the foregoing activities the skilled artisan cannot envision all the detailed chemical structure of the claimed polypeptides (with up to 95% identity), regardless of the complexity or simplicity of the method of isolation.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Therefore, only the isolated polypeptide G45R of SEQ ID NO: 2 or amino acids 24 thru 189 of SEQ ID NO: 2 or sequences that have 95-99% identity to SEQ ID NO: 2

or amino acids 24 thru 189 of SEQ ID NO: 2, with substitutions at wild-type positions generating SNPs wherein the resulting polypeptide exhibits antiviral activity against vesicular stomatitis virus (VSV) *in vitro* or antiviral activity against Encephalomyocarditis virus (EMCV) *in vivo* (mouse model) or dendritic cell maturation or cytokine release by CD4+ or CD8+ T-lymphocytes or cytokine release by monocytes or cellular antiproliferative activity on Daudi Burkitt's cell lines or cellular antiproliferative activity on TF-1 cell lines and any combination of the foregoing activities but not the full breadth of the claims (with all possible amino acids changed) meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. As a result, it does not appear that the inventors were in possession of various polypeptide sequences set forth in claims 27, 28, 42, 48, 51-58, 60, 61, 64 and 65.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

11b. Claims 27, 28, 42, 48, 51-58, 60, 61, 64 and 65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated polypeptide G45R of SEQ ID NO: 2 or amino acids 24 thru 189 of SEQ ID NO: 2 or sequences that have 95-99% identity to SEQ ID NO: 2 or amino acids 24 thru 189 of

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SEQ ID NO: 2, with substitutions at wild-type positions generating SNPs wherein the resulting polypeptide exhibits antiviral activity against vesicular stomatitis virus (VSV) *in vitro* or antiviral activity against Encephalomyocarditis virus (EMCV) *in vivo* (mouse model) or dendritic cell maturation or cytokine release by CD4+ or CD8+ T-lymphocytes or cytokine release by monocytes or cellular antiproliferative activity on Daudi Burkitt's cell lines or cellular antiproliferative activity on TF-1 cell lines and any combination of the foregoing activities (examples 3-6), the disclosure does not reasonably provide enablement for all variants or portions of SEQ ID NO: 2 or amino acids 24 through 189 of SEQ ID NO: 2 (up to 95%) contemplated and which have any and all activities of SEQ ID NO:2 (anti-viral or anti-tumoral or anti-proliferative or immunomodulatory). In addition, it is also unclear what activity if any will be associated or retained with the specific SEQ ID NO: 2 variants including the mature and the immature forms. It is not clear if these functions are found together in variants or if these functional activities are found individually (see for example, claims 27 and 51). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Despite knowledge in the art for producing variants of a given polypeptide with amino acid deletions, insertions or substitutions the specification fails to provide any guidance regarding the changes/modifications contemplated and yet retain the function(s) of the SEQ ID NO: 2 SNP variants claimed. Furthermore, detailed information regarding the structural and functional requirements of the disclosed variant protein is lacking. Although it is accepted that the amino acid sequence of a polypeptide

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determines its structural and functional properties, predicting a protein's structure and function from mere sequence data remains an elusive task. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex.

While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, *Biochemistry* 29:8509-8517; Ngo et al., 1994, *The Protein Folding Problem and Tertiary Structure Prediction*, pp. 492-495, provided with Office Action of 1/9/2006). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even

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if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The instant disclosure fails to disclose which if any functions of the SEQ ID NO: 2 activities will remain or required after the mutation of the polypeptide.

Although, Applicant has only demonstrated (examples 5-8) antiviral activity against vesicular stomatitis virus (VSV) *in vitro* or antiviral activity against Encephalomyocarditis virus (EMCV) *in vivo* (mouse model) or dendritic cell maturation or cytokine release by CD4+ or CD8+ T-lymphocytes or cytokine release by monocytes or cellular antiproliferative activity on Daudi Burkitt's cell lines or cellular antiproliferative activity on TF-1 cell lines for G45R SNP of SEQ ID NO: 2, claims broadly recite anti-viral, anti-tumoral, anti-proliferative and immunomodulatory activities all variants. Therefore, predicting which variants would retain the functions (activities) of the protein is well outside the realm of routine experimentation. Thus, undue amount of experimentation would be required to generate changes/modifications contemplated and yet retain the function of the proteins claimed.

Applicants have not taught how one of skill in the art would use the full scope of polypeptide sequences encompassed by the invention of claims 27, 28, 42, 48, 51-58, 60, 61, 64 and 65. The specification as filed does not sufficiently teach one of skill in the art how to make and/or use the full scope of the claimed sequences. The amount of

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experimentation required to make and/or use the full scope of the claimed sequences would require trial and error experimentation to determine the functional sequences. Given the breadth of claims 27, 28, 42, 48, 51-58, 60, 61, 64 and 65 in light of the unpredictability of the art as determined by the lack of working examples and shown by the prior art of record, the level of skill of the artisan, and the lack of guidance provided in the instant specification, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 112, 1st paragraph, maintained

12. The rejection of claim 37 under 35 U.S.C. 112, first paragraph, as lacking enablement is maintained and added to new claims 64 and 65. Applicant amended the claims to recite several viral diseases and asserts that these diseases maybe treated by the polypeptide of the instant invention. Applicant's arguments have been fully considered. However, there is no evidence that interferon α -17 and in particular G45R SNP of interferon α -17 will have the antiviral activity to treat as chronic hepatitis B, chronic hepatitis C, infectious pneumonias, venereal diseases, or genital warts. The only *in vivo* data provided demonstrates antiviral effect against ECMV virus. Therefore, the rejection of record is maintained. (see below for reapplication of the rejection). Claims 37, 64 and 65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for treating (antiviral activity against vesicular stomatitis virus (VSV) *in vitro*, Encephalomyocarditis virus (EMCV) *in vivo* (mouse model) and against Encephalomyocarditis virus (EMCV) *in vivo* and anti proliferative effect on Daudi

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Burkitt's lymphoma cell line and TF-1 erythroleukemia cell line, does not reasonably provide enablement for the treatment or prevention of cancers or tumors including metastasizing renal carcinomas, melanomas, lymphomas comprising follicular lymphomas and cutaneous T cell lymphoma, leukemias comprising hairy-cell leukemia, chronic lymphocytic leukemia and chronic myeloid leukemia, cancers of the liver, neck, head and kidneys, multiple myelomas, carcinoid tumors and tumors that appear following an immune deficiency comprising Kaposi's sarcoma in the case of AIDS and viral diseases such as chronic hepatitis B, chronic hepatitis C, infectious pneumonias, venereal diseases, or genital warts. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 37, 64 and 65 are drawn to treating or preventing cancers or tumors including metastasizing renal carcinomas, melanomas, lymphomas comprising follicular lymphomas and cutaneous T cell lymphoma, leukemias comprising hairy-cell leukemia, chronic lymphocytic leukemia and chronic myeloid leukemia, cancers of the liver, neck, head and kidneys, multiple myelomas, carcinoid tumors and tumors that appear following an immune deficiency comprising Kaposi's sarcoma in the case of AIDS and viral diseases such as chronic hepatitis B, chronic hepatitis C, infectious pneumonias, venereal diseases, or genital warts by administering a polypeptide with G45R SNP of SEQ ID NO: 2. Applicants have evaluated the antiviral and antiproliferative activity of the interferon polypeptide of SEQ ID NO: 2 comprising the G45R mutation (pages 45-50). Specifically, Applicants demonstrate antiviral activity against vesicular stomatitis

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virus (VSV) *in vitro* and against Encephalomyocarditis virus (EMCV) *in vivo* and anti proliferative effect on Daudi Burkitt's lymphoma cell line and TF-1 erythroleukemia cell line. However, the specification as filed is insufficient to enable one of skilled in the art to practice the claimed invention of treating or preventing all cancers, tumors including metastasizing renal carcinomas, melanomas, lymphomas comprising follicular lymphomas and cutaneous T cell lymphoma, leukemias comprising hairy-cell leukemia, chronic lymphocytic leukemia and chronic myeloid leukemia, cancers of the liver, neck, head and kidneys, multiple myelomas, carcinoid tumors and tumors that appear following an immune deficiency comprising Kaposi's sarcoma in the case of AIDS and viral diseases such as chronic hepatitis B, chronic hepatitis C, infectious pneumonias, venereal diseases, or genital warts without an undue amount of experimentation because the specification and the prior art have not treated or prevented all cancers, tumors including metastasizing renal carcinomas, melanomas, lymphomas comprising follicular lymphomas and cutaneous T cell lymphoma, leukemias comprising hairy-cell leukemia, chronic lymphocytic leukemia and chronic myeloid leukemia, cancers of the liver, neck, head and kidneys, multiple myelomas, carcinoid tumors and tumors that appear following an immune deficiency comprising Kaposi's sarcoma in the case of AIDS and viral diseases such as chronic hepatitis B, chronic hepatitis C, infectious pneumonias, venereal diseases, or genital warts using polypeptide of SEQ ID NO: 2 with G45R SNP.

Applicant has not disclosed how to use the claimed invention to treat or prevent all cancers, tumors and prevent viral diseases of the subjects. There is insufficient

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evidence of the invention with respect to the *in vivo* operability of the claimed invention. In addition, there is no guidance provided in choosing the treatment regimen with therapeutically effective amount for administering to the subjects. Pharmaceutical therapies are unpredictable for the following reasons; (1) the proteins may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half life protein; (2) the protein may otherwise not reach the target area because, for example, the protein may not be able to cross the mucosa; (3) other functional properties, known or unknown, may make the protein unsuitable for *in vivo use*, i.e. may produce adverse side effects prohibitive to the using of such treatment.

Since, there is inadequate guidance as to the nature of the invention, it is merely an invitation to the artisan to use the current invention as a starting point for further experimentation for preventing or treating all cancers, tumors and preventing viral diseases by administering the polypeptide of the instant invention. In addition, because there are no examples provided describing diseases or models it would require an undue amount of experimentation to one of skill in the art to practice the claimed invention.

Given the breadth of claims 37, 64 and 65 in light of the unpredictability of the art as determined by the lack of working examples, the level of skill of the artisan, and the lack of guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention of treating or preventing all cancers or tumors including metastasizing

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renal carcinomas, melanomas, lymphomas comprising follicular lymphomas and cutaneous T cell lymphoma, leukemias comprising hairy-cell leukemia, chronic lymphocytic leukemia and chronic myeloid leukemia, cancers of the liver, neck, head and kidneys, multiple myelomas, carcinoid tumors and tumors that appear following an immune deficiency comprising Kaposi's sarcoma in the case of AIDS and viral diseases such as chronic hepatitis B, chronic hepatitis C, infectious pneumonias, venereal diseases, or genital warts by administering interferon polypeptide of SEQ ID NO: 2 with G45R SNP.

Conclusion

13. No Claims are allowable.

14. Claim 40 directed to the invention(s) of 15 of the restriction mailed 6/21/05 does not require all the limitations of an allowable product claim, and is NOT been rejoined.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon, Ph.D whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published

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applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JS
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May 11th, 2007.

Gregory S. Schuy
Patent Examiner